

less wetness. This overall improvement is presumably explained by placebo effect and spontaneous remission rate. The failure of maximum bladder capacities to show any substantial increase corresponding to this improvement is further evidence of the unsatisfactory nature of this measure.^{3 6}

Our trial suggests that imipramine, which is potentially dangerous because of the risks of accidental or deliberate overdose, should not be used for the treatment of children with diurnal enuresis.

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Familial benign copper deficiency

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SUMMARY Hypocupraemia with normal caeruloplasmin levels was found in a 21-month-old boy admitted to hospital because of repeated seizures and failure to thrive. He had blonde curly hair, spurring of the femora and tibiae, and mild anaemia, but his mental development, electroencephalogram, and structure of the hair on microscopical examination were normal. There was a general improvement in his condition with supplements of oral copper but as soon as these were reduced or stopped hypocupraemia and seizures resumed. Family investigation showed copper deficiency with mild symptoms in the mother and the maternal uncle. The pedigree suggests possible autosomal dominant or X-linked dominant transmission.

Although several conditions leading to sporadic copper deficiency have been described, only two diseases, Wilson's hepatolenticular degeneration and Menkes's kinky-hair syndrome, are regarded as inherited abnormalities of copper metabolism.¹

We report on what is perhaps a new form of familial hypocupraemia.

Case report

The propositus, birthweight 2.95 kg, had a normal delivery and no perinatal complications. At age 6

months he was admitted to hospital because of a seizure and subsequent hypotonia. On admission there were no abnormal physical, neurological, or biochemical findings except for moderate anaemia. Serum copper level was not determined. As there were no symptoms he was discharged 6 days later.

During the next year, although his psychomotor development was good, weight gain was poor and he had frequent infections.

At age 21 months he was referred to our department because of seizures and hypotonic attacks. On admission his weight was below the 3rd centile, but height and head circumference were between the 10th and 25th centiles. His appearance was characteristic with a broad nasal bridge, Cupid's bow upper lip, and blonde curly hair (Fig. 1). The skin on his face was moderately seborrhoeic. Muscle tone, mental development, electroencephalogram, and eyes were normal. Radiological skeletal survey showed broadening and spurring of the femora and tibiae. Skeletal age corresponded to the chronological age. On microscopical examination the child's hair showed normal structure.

Levels of serum glucose, electrolytes, pH, calcium, magnesium, zinc, immunoglobulins, hepatic and renal function tests, urine analysis, blood and urine amino-acid chromatography, glycosaminoglycan excretion were all normal. Stool bacteriology



Fig. 1 Appearance of the propositus at age 21 months.

and parasitology were negative. Haematological studies showed hypochromic anaemia: Hb 10.5 g/dl, haematocrit 32%, white blood count $10.5 \times 10^9/l$, platelets $180 \times 10^9/l$. The serum iron level was extremely low, 4.6 $\mu\text{mol/l}$ (25.7 $\mu\text{g}/100\text{ ml}$). The serum copper concentrations were also very low, 7.8 and 7.0 $\mu\text{mol/l}$ (49.7 and 44.6 $\mu\text{g}/100\text{ ml}$), but caeruloplasmin levels were repeatedly normal, 0.30 to 0.44 g/l. Urinary copper excretion proved to be 26.4 $\mu\text{g}/24\text{ h}$ (0.4 $\mu\text{mol}/24\text{ h}$). (Normal values in our laboratory: serum iron 9.5–26.8 $\mu\text{mol/l}$, serum copper 12.4–20.0 $\mu\text{mol/l}$, caeruloplasmin 0.30–0.56 g/l, urinary copper excretion 15–45 $\mu\text{g}/24\text{ h}$ for children, and 20–130 $\mu\text{g}/24\text{ h}$ for adults.) Copper concentrations were measured by means of atomic absorption spectrophotometry, caeruloplasmin by a radial immunodiffusion method.

Since the clinical picture correlated well with hypocupraemia, we started the patient on supplements of oral copper in the form of copper sulphate syrup. The results and course of treatment are shown in Fig. 2.

Supplements of 7.5 mg elementary copper per 24 hours kept the serum copper level normal. If this dose was reduced or stopped concentrations were again very low and the child became unconscious for short periods and seizures were resumed; twice he had hypotonia. With copper supplements the child thrived and his weight reached the 10th centile. At age 40 months his IQ was 104, and the electroencephalogram normal. Although he received no iron therapy, the anaemia disappeared, the serum iron levels increased after 2 months of copper

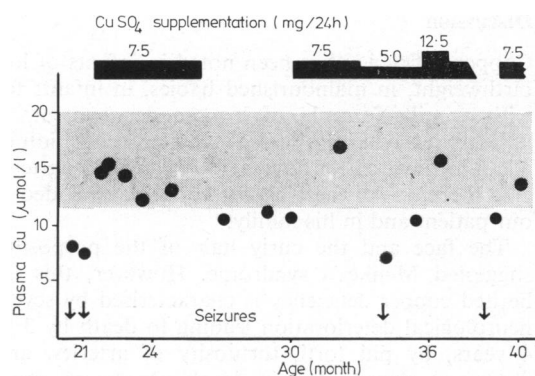


Fig. 2 Effect of copper supplementation on plasma copper level and neurological symptoms of the patient.

supplementation to 11.2–27.0 $\mu\text{mol/l}$ (62.6–150.8 $\mu\text{g}/100\text{ ml}$) with normal TIBC values. The copper content of the hair was first measured at that time; it proved to be high, 62.4 $\mu\text{g/g}$.

Family investigation

Seven family members were examined and biochemically tested.

The father and the two brothers were physically and biochemically normal. Their serum copper levels varied between 20.9 and 23.5 $\mu\text{mol/l}$ (133 and 149.7 $\mu\text{g}/100\text{ ml}$).

The mother of our patient was a 28-year-old, conspicuously thin woman. She had always been pale and susceptible to recurrent infections but she had never had seizures. Her face was seborrhoeic, the hair thin. She complained of increasing loss of hair, in consequence of which she was almost bald at the top of the head. Serum copper levels were subnormal, 11.0 and 10.4 $\mu\text{mol/l}$ (70 and 66 $\mu\text{g}/100\text{ ml}$), Hb 11.3 and 11.0 g/dl, urinary copper output 128.0 $\mu\text{g}/24\text{ h}$ (2 $\mu\text{mol}/24\text{ h}$). The copper content of her hair was moderately decreased, 13.0 $\mu\text{g/g}$.

The mother's brother was also thin. As a child he had often been ill, but had never had seizures. He had had blonde, extremely curly hair, but had been bald since aged about 24 years. His skin was seborrhoeic. His serum copper level was 10.4 $\mu\text{mol/l}$ (66 $\mu\text{g}/100\text{ ml}$), caeruloplasmin 0.36 g/l. His two sons were healthy; they had no seizures, and their hair was brown and slightly curly. Their serum copper concentrations varied between 13.4 and 17.0 $\mu\text{mol/l}$ (85.4 and 108 $\mu\text{g}/100\text{ ml}$).

The diet of the family members was mixed, and certainly contained satisfactory quantities of copper, iron, and vitamins.

Discussion

Copper deficiency has been noted in infants of low birthweight, in malnourished babies, in infants fed with a milk formula of low copper content, in patients receiving prolonged parenteral nutrition or alkali medication for renal acidosis, or on long-term zinc therapy. All these causes could be excluded in our patient and in his family.

The face and the curly hair of the propositus suggested Menkes's syndrome. However, this inherited copper deficiency is characterised by severe neurological deterioration leading to death by 3 to 4 years, by pili torti, tortuosity of arteries, and decreased caeruloplasmin levels. None of these features was found in our patient, and in Menkes's syndrome oral administration of copper is generally ineffective.² Considering the normal mental development and the normal caeruloplasmin levels of the child, his condition does not correspond to the 'mild form of Menkes's syndrome'³ nor does it correspond to so called pseudo-Menkes's syndrome.^{4,5}

We were not able to clarify the mechanism of copper deficiency in the family reported here. Excessive renal loss of copper and insufficient dietary intake could be ruled out, and the underlying cause is probably a defect in the absorption of copper. Considering the mild and reversible symptoms the mechanism must certainly differ from that of true Menkes's syndrome.^{6,7}

The inheritance of copper deficiency in the family examined may represent an autosomal or an X-linked dominant trait.

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Pseudohypoaldosteronism. Response to long-term treatment with indomethacin

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SUMMARY A 6-month-old boy presented with features of pseudohypoaldosteronism. Considerable quantities of supplemental sodium failed to compensate his natriuresis but indomethacin, a prostaglandin inhibitor, greatly reduced his sodium requirement. Treatment was maintained for 9 months when re-evaluation showed him to be dependent on indomethacin for satisfactory control.

A boy of consanguineous Saudi-Arabian parents, birthweight 3 kg, presented from a few weeks of age with lethargy, vomiting, recurrent hyponatraemic, hyperkalaemic dehydration (for example serum

sodium 109 mmol/l, potassium 7 mmol/l). There was no response to 15 µg/24 h 9α-fludrocortisone or to 2 mg/24 h DOCA but large supplements of sodium corrected the biochemical abnormalities.

He was referred to us aged 6 months, weighing 4.8 kg. Apart from a slightly raised (110/65 mmHg) blood pressure (BP) his clinical condition was normal. The principal biochemical findings are shown in the Table. Levels of urinary urea, creatinine, calcium, and phosphate, and amino-acid excretion were normal.

During a vomiting, hyponatraemic episode his resistance to 30 µg/24 h 9α-fludrocortisone was demonstrated and it was with difficulty that the